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NAME CHANGE

MINISTRY OF ECONOMIC AFFAIRS

PATENT OF INVENTION

The Minister of Economic Affairs,

Considering the Patent Law of May 24, 1854;

Considering the Unification Treaty for the Protection of Industrial Property;

Considering the report on March 20, 1961, at 3:30 p.m.

to the District Commissioner of Turnhout;

DECIDES:

Article 1. – *A patent of invention is granted to* Paul A. J. JANSSEN,

Antwerpse steenweg, 30, Vosselaar,

represented by Ludo J.M. Van Bauwel, Beerse Heide, 1, Gierle,

for: New 1-aroylalkyl-4-arylpiperidinecarboxamides and methods for their production,

which they declare to have been the subject of a patent application filed in the United States of America on March 14, 1960.

Article 2. - *This patent is granted to him without prior examination, on his own responsibility, without guarantee of either the significance, novelty or merits of the invention or the accuracy of the description, and without prejudice to the rights of third parties.*

A copy of the description and drawings of the invention, signed by the interested party and filed in support of the application, must remain attached to this decision.

Brussels, March 31, 1961.
BY SPECIAL AUTHORIZATION:
J. HAMELS
601228

Description

Pertaining to the

Patent Application

of

Dr. Paul Adriaan Jan Janssen, Vosselaar,

to obtain a Patent of Invention entitled:

"New 1-aroylalkyl-4-arylpiperidinecarboxamides, as well as methods for their production"

For which invention a priority claim is made, stemming from a first patent application, filed March 14, 1960 in the name of the same applicant with the United States Patent Office in Washington, United States of America, and entered there under No. 14,570.

New 1-aroylalkyl-4-arylpiperidinecarboxamides, as well as methods for their production.

This invention concerns a new series of 1-aroylalkyl-4-arylpiperidinecarboxamides with the following formula:

[please refer to figure in original document -- translator's note]

in which Ar is a member of the class consisting of phenyl, lower alkylphenyl, xylyl, halophenyl, methoxyphenyl and thienyl radicals;

Ar' is a member of the class consisting of phenyl, lower alkylphenyl, xylyl, halophenyl, methoxyphenyl and trifluoromethylphenyl radicals;

Alk is a lower alkylene radical with at least 3 carbon atoms;

X is a member of the class consisting of hydrogen and a methyl radical; and

R is a member of the class consisting of a primary, secondary or tertiary amino radical.

Typical examples of the lower alkylphenyl series, which Ar and Ar' can represent, are tolyl, ethylphenyl, amyl and the like.

The radical Alk represents a lower alkylene radical with at least 3 carbon atoms comprising trimethylene, propylene, butylene, methylpropylene, tetramethylene and

pentamethylene. Substances in which Alk is a trimethylene radical may be mentioned, in particular, in this invention.

The primary, secondary and tertiary amino radicals – represented by R – are members of the class consisting of $-NH_2$, $-N(CH_3)$-phenyl, aniline, benzylamino, pyrrolidino, piperidino, morpholino, methylmorpholino, dimethylmorpholino, piperazino and phenylpiperazino radicals. R can also represent radicals with the formula NH (lower alkyl) and N (lower alkyl)$_2$, in which the lower alkyl radical represents methyl, ethyl, branched or unbranched propyl, butyl, amyl or hexyl.

The described substances have powerful biological properties as apomorphine inhibitors and therefore potentiate barbiturates. In therapeutic amounts they exhibit little or no Parkinson-like side effects, hypnosis and cortical inhibition. They are therefore very useful as special anti-emetics.

The organic bases of this invention form pharmaceutically acceptable salts with a variety of inorganic and strong organic acids, like sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid, tartaric acid, cinnamic acid, citric acid, benzoic acid, gluconic acid, ascorbic acid and related acids.

They also form quaternary ammonium salts with a variety of organic esters of sulfuric acid, hydrohalic acids and aromatic sulfonic acids. Methyl chloride and bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride and bromide, phenethyl bromide, naphthylmethyl chloride, dimethyl sulfate, diethyl sulfate, methylbenzene sulfonate, ethyltoluene sulfonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide and crotyl bromide are among these esters.

The substances of this invention can be prepared by condensation of an aroylalkyl halide with the formula:

Ar-CO-Alk-halogen

with an appropriately chosen 4-arylpiperidinecarboxamide

[please refer to figure in original document -- translator's note]

in which a substance with the following formula is obtained:

[please refer to figure in original document -- translator's note]

in which Alk, Ar, Ar', R and X have the aforementioned meaning. The reaction can be run in an inert solvent, like an aromatic hydrocarbon, for example, benzene, toluene, xylene, a lower

[please refer to figure in original document -- translator's note]

is obtained, in which and Y have the aforementioned meaning (when Y is a benzyl radical, this substance is obtained as the hydrochloride).

A mixture of 0.46 mol of the aforementioned dichloride in about 2.5 mol toluene and 1 mol sodium amide is heated to about 45°C. About 0.43 mol of a nitrile with the formula

$$Ar'\text{-}CH_2\text{-}CN$$

is then added batchwise, in order to control the exothermic reaction. When Ar' is thienyl, a different method is used to combine the initial products. The nitrile with the formula

[please refer to figure in original document -- translator's note]

is added to an agitated and cooled suspension of sodium amide and toluene. A solution of the dichloride in toluene is then added batchwise to this mixture, whereupon the temperature rises to about 47°C. This mixture is then slowly heated to the boiling point and kept at this temperature for 1 to 5 hours. After cooling to 0°C, the mixture is decomposed with water. The solid precipitate is collected on a filter and dried, obtaining a substance with the formula

[please refer to figure in original document -- translator's note]

in which Y, X and Ar' have the aforementioned meaning.

The substances in which X is hydrogen can be purified by crystallization from water and methanol. If Y is benzyl, the hydrochlorides of these substances are prepared by treating a solution of the substance with HCl gas and collecting the precipitate. Characteristic substances have the following physical constants:

1-benzyl-4-cyano-4-(3-tolyl)piperidine hydrochloride; mp about 247.5 – 249.3°C

1-benzyl-4-cyano-4-(4-tolyl)piperidine hydrochloride; mp about 281.6 – 282.9°C

1-(4-toluenesulfonyl)-4-cyano-4-(3-chlorophenyl)piperidine; mp about 179.6 – 180.4°C

1-(4-toluenesulfonyl)-4-cyano-4-(3-tolyl)piperidine; mp about 190 - 191°C

1-(4-toluenesulfonyl)-4-cyano-4-(2-thienyl)piperidine; mp about 149.8 - 160°C with decomposition.

alkanol, e.g., ethanol, propanol, butanol, or a lower alkanone, e.g., acetone, butanone, pentanone or hexanone. An extraordinarily useful solvent for preparation is 4-methyl-2-pentanone. The performed reaction can be accelerated by using higher temperatures.

The aroylalkyl halides employed as intermediates can best be prepared by means of the Friedel-Crafts reaction (including its milder variation), in which γ-chlorobutyryl chloride and benzene or a suitably substituted benzene, like toluene and xylene, a halogenated benzene, like chlorobenzene, bromobenzene and fluorobenzene, or an alkoxybenzene, like anisole and phenetole, are used.

These intermediates can also be prepared by treatment of an ω-haloalkanonitrile with a suitable alkylmagnesium bromide, followed by hydrolysis of the conversion product.

The substances with the formula

[please refer to figure in original document -- translator's note]

in which Ar', R and X have the aforementioned meaning and are used as intermediates in the aforementioned preparation method, are prepared as follows:

A mixture of 1 mol of the following substance $HO\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}CH_2\text{-}CH(X)\text{-}OH$ and 0.5 mol sodium carbonate in a 2N aqueous solution is first heated to about 70 - 95°C. 1 mol of substance Y-Cl is added at this temperature, in which X has the meaning mentioned above and Y is a radical capable of protecting the nitrogen atom, like p-toluenesulfonyl or benzyl. The mixture is heated to about 95°C over 1 hour. After extraction with ether, the solvent is evaporated and the residue dissolved in 2-propanol. Ether is added and the mixture is cooled. The solid that precipitates is collected on a filter and dried, so that a substance with the formula

[please refer to figure in original document -- translator's note]

is obtained, in which X and Y have the aforementioned meaning.

When X is a methyl radical and Y a 4-toluenesulfonyl radical, the substance can be purified by crystallization from a 1:3 mixture of ethanol and acetone. The N-(β-hydroxyethyl)-N-(β-hydroxypropyl)-4-toluenesulfamide so obtained melts at about 66.2 -- 68.2°C.

A mixture of 1.73 mol of the aforementioned product and 6 mol thienyl chloride are heated over 1 hour to about 125°C and then cooled. The excess thienyl chloride is evaporated and the residue dissolved in toluene, filtered and evaporated, so that a substance with the formula

When X is a methyl radical, 2 optically active stereoisomers are formed. For preparation of these substances, precisely the same preparation method as stated above is followed; the isomers are separated by fractional crystallization, typically from acetone. In the following description, the isomer that forms at the beginning of this partial crystallization is referred to as α and the second isomer as β. This terminology has nothing to do with the actual configuration of the molecule. Typical substances obtained in this manner are:

1-(4-toluenesulfonyl)-3α-methyl-4-cyano-4-(4-chlorophenyl)piperidine; mp about 205 - 206°C

1-(4-toluenesulfonyl)-3α-methyl-4-cyano-4-(4-fluorophenyl)piperidine; mp about 141.8 – 142.8°C

1-(4-toluenesulfonyl)-3β-methyl-4-cyano-4-(4-fluorophenyl)piperidine; mp about 204.5 – 205.5°C

1-(4-toluenesulfonyl)-3α-methyl-4-cyano-4-(4-tolyl)piperidine; mp about 209.5 – 210.2°C

1-(4-toluenesulfonyl)-3α-methyl-4-cyano-4-phenyl-piperidine; mp about 146.2 - 148°C

1-(4-toluenesulfonyl)-3β-methyl-4-cyano-4-phenyl-piperidine; mp about 217 - 218°C.

The preceding nitriles can be directly hydrolyzed with acid, forming the carboxamides. In this method of preparation, a mixture of 6 parts nitrile, 18 parts concentrated sulfuric acid and about 1 part water are heated for over 15 hours to about 100°C. The mixture is then poured into ice water, made alkaline and extracted with chloroform. The extract is dried, producing the base of the substance with the formula

[please refer to figure in original document -- translator's note]

When one intends to obtain the hydrochloride, the base is dissolved in an appropriate organic solvent, like acetone and ether. The solution is then saturated with HCl gas. The hydrochloride that precipitates can then be purified by recrystallization from 2-propanol. Substances obtained in this way are:

3α-methyl -4-phenylpiperidine-4-carboxamide hydrochloride, with mp about 206.5 - 211°C

When Y is a toluenesulfonyl radical, the following reaction is used. A suspension of 0.25 mol of the acid

[please refer to figure in original document -- translator's note]

2 mol thienyl chloride and 5 mol benzene is boiled under reflux for 2 hours, cooled and filtered. After decoloring with activated charcoal, the solution is evaporated and the solid residue can be purified by trituration with petroleum ether. The substance has the following formula:

[please refer to figure in original document -- translator's note]

1.5 mol of a substance with the formula HR, in which R has the aforementioned meaning, is added batchwise during cooling to an agitated solution of this acid halide in benzene. After addition is complete, the mixture is kept for 10 hours at room temperature and the solid precipitate collected, producing a substance with the following formula:

[please refer to figure in original document -- translator's note]

The following typical substances are obtained in this way:

1-(4-toluenesulfonyl)-3α-methyl-4-phenylpiperidine-4-(N-methyl)carboxamide; mp about 219.5 – 221.3°C

1-(4-toluenesulfonyl)-4-(4-chlorophenyl)-piperidine-4-(N,N,-dimethyl)carboxamide; mp about 159.4 - 163°C

1-(4-toluenesulfonyl)-4-(4-fluorophenyl)-4-carboxypiperidine pyrrolidide; mp about 227 - 232°C

1-(4-toluenesulfonyl)-4-(4-methoxyphenyl)-4-carboxypiperidine pyrrolidide; mp 174.5 - 176°C

1-(4-toluenesulfonyl)-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide; mp about 239.5 – 241.5°C

1-(4-toluenesulfonyl)-3α-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide; mp about 186.6 – 187.4°C

3β-methyl-4-phenylpiperidine-4-carboxamide, with mp about 190 – 192.8°C

3β-methyl-4-phenylpiperidine-4-carboxamide hydrochloride, with mp about 296.5 - 299°C.

For preparation of substituted amides, a different reaction sequence is used. A mixture of 1 part of the aforementioned nitrile, 1 part potassium hydroxide and 10 parts of a suitable solvent, like methanol, ethanol or ethylene glycol, is heated in an autoclave for 9 hours to about 180°C. After cooling, the mixture is decolored and then evaporated. The residue is dissolved in water and the solution made alkaline. The solid precipitate is collected on a filter and then purified with boiling water; the acid with the formula

[please refer to figure in original document -- translator's note]

is formed by this.

The substances obtained in this way are:

1-(4-toluenesulfonyl)-3α-methyl-4-phenyl-4-carboxypiperidine; mp about 173.5 - 175°C

1-(4-toluenesulfonyl)-3β-methyl-4-phenyl-4-carboxypiperidine; mp about 209.5 – 211.4°C

1-(4-toluenesulfonyl)-4-(2-(thienyl)-4-carboxypiperidine; mp about 216.6 - 219°C

1-(4-toluenesulfonyl)-3α-methyl-4-(4-chlorophenyl)-4-carboxypiperidine; mp about 177 - 179°C

1-(4-toluenesulfonyl)-4-(4-chlorophenyl)-4-carboxypiperidine; mp about 221 – 222.5°C

1-(4-toluenesulfonyl)-4-(4-tolyl)-4-carboxypiperidine; mp about 226.5 – 228.5°C

1-benzyl-4-(4-tolyl)-4-carboxypiperidine; mp about 280 - 283°C

1-benzyl-4-(4-chlorophenyl)-4-carboxypiperidine hydrochloride; mp about 257.9 - 261°C

When Y is benzyl, the substituted amides are prepared by boiling under reflux for 2 hours at 0.25 mol of the aforementioned acid and 2 mol thienyl of chloride.

After evaporation of the excess thienyl chloride, the residue is treated with benzene. The solid precipitate is collected on a filter, finely distributed and suspend in benzene. The suspension is cooled and 1.25 mol of the substance with the formula HR, in which R has the aforementioned meaning, is added batchwise over 15 minutes. The mixture is then allowed to

cool to room temperature, agitated over 12 hours and made alkaline. After extraction with a benzene-ether mixture, the extract is dried and evaporated. The solid residue is a substance with the following formula:

[please refer to figure in original document -- translator's note]

in which Ar', R, X and Y have the aforementioned meaning. The following particular substances are obtained in this way:

1-benzyl-4-(4-tolyl)-4-carboxypiperidine morpholide; mp about 136.6 – 138.7°C

1-benzyl-4-(4-tolyl)-piperidine-4-(N,N-dimethyl)carboxamide; mp about 136.4 – 140.1°C

1-benzyl-4-phenylpiperidine-4-(N-methyl)-N-carboxy-anilinde hydrochloride; mp about 220 - 221°C

1-benzyl-4-(3-tolyl)-4-carboxypiperidine pyrrolidide; mp about 105 - 108°C

1-benzyl-4-(4-tolyl)-4-carboxypiperidine pyrrolidide; mp about 155 - 156°C

1-benzyl-4-(3-tolyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 95.4 – 98.6°C

1-benzyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide, mp about 73.4 – 74.6°C

1-benzyl-4-(3-tolyl)-4-carboxypiperidine morpholide; mp about 156 - 158°C

1-benzyl-4-(4-tolyl)-4-carboxypiperidine piperidide; mp about 121 – 121.5°C

1-benzyl-4-phenylpiperidine-4-(N-benzyl)carboxamide; mp about 129.5 – 130.5°C

1-benzyl-4-phenylperidine-4-(N-phenyl)carboxamide hydrochloride; mp about 261.0 – 262.5°C

1-benzyl-4-phenyl-4-carboxypiperidine pyrrolidide; mp about 165.5 – 166.5°C

1-benzyl-4-phenyl-4-carboxypiperidine morpholide; mp about 138.2 – 139.8°C

1-benzyl-4-phenyl-4-carboxypiperidine piperidide; mp about 132.8 - 134°C

1-benzyl-4-phenylpiperidine-4-(N-methyl)carboxamide; mp about 135.2 – 136.4°C

1-benzyl-4-phenylpiperidine-4-(N-tert-butyl)carboxamide; mp about 127.4 – 128.2°C

1-benzyl-4-(4-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 141 – 142.8°C

1-benzyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide; mp about 137 - 138°C

1-(4-toluenesulfonyl)-3β-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide; mp about 194 - 195°C

1-(4-toluenesulfonyl)-3β-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide; mp about 161.8 - 163°C

1-(4-toluenesulfonyl)-3α-methyl-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide; mp about 152 - 154°C

1-(4-toluenesulfonyl)-3β-methyl-4-phenyl-4-carboxypiperidine pyrrolidide; mp about 184.2 - 185°C

1-(4-toluenesulfonyl)-3β-methyl-4-phenyl-4-carboxypiperidine piperidide; mp about 189.4 - 190°C

1-(4-toluenesulfonyl)-3α-methyl-4-phenyl-4-carboxypiperidine morpholide; mp about 149 – 150.5°C

1-(4-toluenesulfonyl)-4-(2-thienyl)-4-carboxypiperidine

1-(4-toluenesulfonyl)-3α-methyl-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide

1-(4-toluenesulfonyl)-4-(3-chlorophenyl)-piperidine-4-(N,N-dimethyl)carboxamide; mp about 152 - 156°C

1-(4-toluenesulfonyl)-4-(4-ethylphenyl)-4-carboxypiperidine pyrrolidide; mp about 131.2 - 133°C

1-(4-toluenesulfonyl)-4-(3-methoxyphenyl)-4-carboxypiperidine pyrrolidide; mp about 164.6 – 167.6°C with decomposition

1-(4-toluenesulfonyl)-4-(4-fluorophenyl)-4-carboxypiperidine morpholide; mp about 219.5 - 221°C

1-(4-toluenesulfonyl)-4-(3-methoxyphenyl)-piperidine-4-(N,N-dimethyl)carboxamide; mp about 147 – 151.6°C

1-(4-toluenesulfonyl)-4-(4-fluorophenyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 87 - 133°C.

The amides of the last formula can be easily converted to their analogs, which are unsubstituted on the piperidine nitrogen in 1 or 2 ways.

The first method to eliminate the protecting group Y is chosen when Y is a 4-toluenesulfonyl radical. A mixture of 1 part of the aforementioned amide, 1 part phenol and 10

parts of a 30% solution of hydrogen bromide in acetic acid is agitated at room temperature for 20 hours and then distributed between ether and water. The aqueous solution is eliminated, made alkaline and then extracted with chloroform. The chloroform extract is dried and then evaporated. The residue can be purified, producing a base with the following formula:

[please refer to figure in original document -- translator's note]

or it can be dissolved in ether. The solution is saturated with HCl gas. The solid hydrochloride precipitate can then be collected on a filter. The following typical substances can be obtained in this way:

3α-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 252.4 - 255°C

3α-methyl-4-phenyl-4-carboxypiperidine piperidide hydrochloride; mp about 236.5 – 238.5°C

3α-methyl-4-phenyl-4-carboxypiperidine morpholide; mp about 111.5 - 114°C

3α-methyl-4-phenyl-4-carboxypiperidine morpholide hydrochloride; mp about 259.6 – 260.8°C

3β-methyl-4-phenyl-4-carboxypiperidine piperidide hydrochloride; mp about 255.8 – 257.6°C

3β-methyl-4-phenyl-4-carboxypiperidine pyrrolidide; mp about 129.2 – 132.4°C

3β-methyl-4-phenyl-4-carboxypiperidine pyrrolidide hydrochloride; mp about 247 - 249°C

3β-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 230 - 231°C

3α-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 243 - 245°C

3β-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide; mp about 123.8 – 124.6°C

3α-methyl-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 268 - 270°C with decomposition

4-(3-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 105 - 106°C

4-phenyl-4-carboxypiperidine-2,6-dimethylmorpholide oxalate; mp about 90 - 152°C with decomposition

4-(4-ethylphenyl)-4-carboxypiperidine pyrrolidide; mp about 109.5 – 110.5°C

4-(3-methoxyphenyl)-4-carboxypiperidine pyrrolidide; mp about 121.5 – 123.8°C

4-(4-fluorophenyl)-4-carboxypiperidine morpholide; mp about 133 - 136°C

4-(3-methoxyphenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp 205 - 206°C

4-(4-fluorophenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 199.5 - 203°C

4-phenyl-4-carboxypiperidine-4-phenylpiperazide; mp about 126 - 129°C

4-(2-thienyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 162 - 211°C

4-phenylpiperidine-4-(N-isopropyl)carboxamide oxalate; mp about 211.5 – 212.5°C

4-(4-fluorophenyl)-4-carboxypiperidine pyrrolidide; mp about 139.6 – 140.4°C

4-(4-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 227 - 228°C

4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide; mp about 146.8 – 147.6°C.

A second preparation method is chosen when Y is benzyl. A mixture of 20 parts of an amide with the following formula

[please refer to figure in original document -- translator's note]

in 150 parts 2-propanol and 50 parts water is hydrogenated at about 30°C in the presence of a palladium/carbon catalyst. After absorption of the calculated amount of hydrogen, the mixture is heated and then filtered. The filtrate is evaporated and the solid residue purified, producing a substance with the formula

[please refer to figure in original document -- translator's note]

The following substances can be produced in this way:

4-phenylpiperidine-4-carboxamide; mp about 154 - 155°C

4-phenylpiperidine-4-(N,N-dimethyl)carboxamide; mp about 74.5 - 81°C

4-(4-tolyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 126 - 130°C

4-(3-tolyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 99.2 – 101.1°C

4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 235.8 – 236.5°C

4-phenylpiperidine-4-(N-tert-butyl)carboxamide hydrochloride; mp about 276.8 - 278°C

4-phenylpiperidine-4-N-carboxyanilide hydrochloride, mp about 218.5 - 222°C

4-phenylpiperidine-4-(N-benzyl)carboxamide hydrochloride; mp about 278 – 279.5°C

4-phenylpiperidine-4-N-methyl-N-carboxyanilide hydrochloride; mp about 275 - 276°C

4-(4-tolyl)-4-carboxypiperidine pyrrolidide; mp about 142.2 – 142.8°C

4-(3-tolyl)-4-carboxypiperidine pyrrolidide; mp about 109 - 110°C

4-phenyl-4-carboxypiperidine pyrrolidide; mp about 126 – 127.4°C

4-phenyl-4-carboxypiperidine pyrrolidide hydrochloride; mp about 229 – 230.5°C

4-phenyl-4-carboxypiperidine morpholide; mp about 125 - 126°C

4-(4-tolyl)-4-carboxypiperidine morpholide; mp about 142 – 142.8°C

4-(3-tolyl)-4-carboxypiperidine morpholide; mp about 110.4 – 111.2°C

4-phenyl-4-carboxypiperidine piperidide; mp about 122 – 123.5°C

4-(4-tolyl)-4-carboxypiperidine piperidide; mp about 104.8 - 107°C

The substances that form the object of this invention, as well as their preparation methods, will be further explained below by means of the following examples:

Example 1

A solution of 71 parts γ-chlorobutyryl chloride and 63 parts benzene are added under agitation and cooling to a suspension of 71 parts aluminum chloride and 310 parts benzene. After addition is complete, the cooling bath is removed and agitation continued for 30 minutes. The reaction mixture is poured into ice water. The benzene layer is separated, dried on anhydrous sodium sulfate and filtered. The filtrate is concentrated under reduced pressure to eliminate the benzene and the residue is distilled, obtaining γ-chlorobutyrophenone, which boils at about 134 - 137°C at 5 mm pressure.

By equimolar substitution of the appropriate starting materials, the following substances are obtained:

ω-chlorohexanophenone

γ,3-dichlorobutyrophenone

γ-chloro-4-methoxybutyrophenone; b_6 = 175°C

γ-chloro-4-iodobutyrophenone

γ-chloro-3-methoxybutyrophenone

γ-chloro-4-fluorobutyrophenone; b_6 = 136 - 142°C

Example 2

A mixture of 5.4 parts γ-chlorobutyrophenone, 6 parts 3α-methyl-4-phenylpiperidine-4-carboxamide, 8.5 parts sodium carbonate, 0.1 part potassium iodide and 200 parts 4-methyl-2-pentanone is boiled for 72 hours under reflux, cooled and filtered. The filtrate is evaporated and the residue dissolved in anhydrous ether. After filtration to eliminate the inorganic salts, HCl gas is passed through the solution. The solid precipitate is collected on a filter, recrystallized from 2-propanol and dried, obtaining 1-(γ-benzoylpropyl)-3α-methyl-4-phenylpiperidine-4-carboxamide hydrochloride; mp about 196.2 – 198.6°C.

Example 3

By substituting appropriate starting materials in the preceding example, the following substances are prepared:

1-(γ-benzoyl)-3β-methyl-4-phenylpiperidine-4-carboxamide hydrochloride; mp about 267.5 - 268°C

1-(γ-benzoylpropyl)-4-phenylpiperidine-4-(N-methyl)carboxamide hydrochloride; mp about 209.5 - 212°C

1-(γ-benzoylpropyl)-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 214.5 – 215.5°C

1-(γ-benzoylpropyl)-3β-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 238 - 239°C

1-(γ-benzoylpropyl)-4-(3-tolyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 200 – 201.4°C;

1-(γ-benzoylpropyl)-4-(4-tolyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 227 – 228.5°C

1-(γ-benzoylpropyl)-4-(4-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 232 - 233°C

1-(ω-benzoylpropyl)-4-(4-chlorophenyl)-piperidine-4-(N,N-dimethyl)carboxamide hydrochloride

1-(γ-benzoylpropyl)-4-phenylpiperidine-4-(N,N-diethyl)carboxamide hydrochloride. Its oxalate melts at about 69.5 – 71.5°C

1-(γ-benzoylpropyl)-3α-methyl-4-phenylpiperidine-4-(N,N-diethyl)carboxamide. Its oxalate melts at about 163 – 167.8°C

1-(γ-benzoylpropyl)-3β-methyl-4-phenylpiperidine-4-(N,N-diethyl)carboxamide hydrochloride; mp about 186.8 – 188.6°C

1-(γ-benzoylpropyl)-4-phenyl-4-carboxypiperidine pyrrolidide hydrochloride; mp about 203 - 204°C. A second fraction obtained by cooling to -20°C, mp about 207 - 209°C

1-(γ-benzoylpropyl)-3α-methyl-4-phenyl-4-carboxypiperidine pyrrolidide. Its oxalate melts at about 171.6 – 174.6°C with decomposition.

1-(γ-benzoylpropyl)-4-(3-tolyl)-4-carboxypiperidine pyrrolidide. Its oxalate melts at about 200 - 203°C with decomposition.

1-(γ-benzoylpropyl)-4-(4-tolyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 200 – 201.5°C

1-(γ-benzoylpropyl)-4-(4-fluorophenyl)-4-carboxypiperidine pyrrolidide. Its oxalate melts at about 206 - 208°C

1-(γ-benzoylpropyl)-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 216 - 218°C

1-(γ-benzoylpropyl)-4-(4-trifluoromethylphenyl)-4-carboxypiperidine pyrrolidide hydrochloride.

1-(γ-benzoylpropyl)-4-phenyl-4-carboxypiperidine piperidide; mp about 132.6 – 133.5°C

1-(γ-benzoylpropyl)-3α-methyl-4-phenyl-4-carboxypiperidine piperidide. Its oxalate melts at about 180.1 - 182°C

1-(γ-benzoylpropyl)-4-phenyl-4-carboxypiperidine morpholide hydrochloride; mp about 285°C with decomposition

1-(γ-benzoylpropyl)-3α-methyl-4-phenyl-4-carboxypiperidine morpholide. Its oxalate melts at about 181.5 – 184.5°C

1-(γ-benzoylpropyl)-3β-methyl-4-carboxypiperidine morpholide hydrochloride; mp about 220.5 – 221.5°C

1-(γ-benzoylpropyl)-4-(3-tolyl)-4-carboxypiperidine morpholide hydrochloride; mp about 244 - 248°C

1-(γ-benzoylpropyl)-4-(4-tolyl)-4-carboxypiperidine morpholide hydrochloride; mp about 224 - 225°C

1-(γ-benzoylpropyl)-4-(4-ethylphenyl)-4-carboxypiperidine morpholide hydrochloride

1-[γ-(4-methoxybenzoyl)propyl]-4-(4-chlorphenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 194 – 195.2°C

1-[γ-(3-methoxybenzoyl)propyl]-4-(4-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride.

Example 4

A mixture of 84 parts thiophene, 141 parts γ-chlorobutyryl chloride and 870 parts benzene is cooled to about 0°C. Maintaining this temperature, 260 parts stannic chloride is added over a period of 2 hours. After addition is completed, the cooling bath is removed and agitation continued for about 1 hour. The reaction mixture is then poured into a mixture of 60 parts concentrated hydrochloride and 450 parts ice water. The organic layer is separated, washed with water, dried on anhydrous calcium chloride and filtered. The filtrate is concentrated under reduced pressure. The residue is distilled, obtaining 2-(γ-chlorobutyryl)thiophene, which boils at 144 - 146°C under a pressure of 11 mm.

Example 5

From 4.9 parts 4-phenylpiperidine-4-(N,N-tert-butyl)carboxamide hydrochloride, the free base is liberated by dissolving 4.9 parts of the salt in water, making the solution alkaline, extracting it with chloroform and evaporating the organic extract. The residue of 5.3 parts sodium carbonate and 0.1 part potassium iodide in 60 parts 4-methyl-2-pentanone is agitated together. 4.3 parts 2-(γ-chlorobutyryl)thiophene in 60 parts 4-methyl-2-pentanone is added batchwise to the solution. After the mixture has been boiled under reflux for 48 hours, it is cooled and washed with water. The organic solution is dried and evaporated. The residue is dissolved in methanol. A solution of oxalic acid, also in methanol, must then be added to the solution. The solid precipitate is collected on a filter and dried, so that 1-[γ-(2-thenoyl)propyl]-4-phenylpiperidine-4-(tert-butyl)carboxamide oxalate is obtained, which melts at about 219 – 220.5°C

Example 6

By substituting equimolar amounts of appropriate starting materials in the previous example, the following substances are obtained:

1-[γ-(2-thenoyl)propyl]-4-phenylpiperidine-4-(N-phenyl)carboxamide. Its oxalate melts at about 217 – 220.8°C with decomposition.

1-[γ-(2-thenoyl)propyl]-4-phenylpiperidine-4-(N-benzyl)carboxamide hydrochloride; mp about 182.4 – 184.2°C

1-[ω-(2-thenoyl)propyl]-4-phenylpiperidine-4-(N-benzyl)carboxamide hydrochloride

1-[γ-(2-thenoyl)propyl]-4-phenylpiperidine-4-(N-methyl)-4-(N-phenyl)carboxamide hydrochloride; mp about 231.6 – 232.5°C

1-[γ-(2-thenoyl)propyl]-3β-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 244 – 245.2°C

1-[γ-(2-thenoyl)propyl]-4-(3-tolyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 206.5 – 207.7°C

1-[γ-(2-thenoyl)propyl]-4-(4-tolyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 242.5 – 243.5°C

1-[γ-(2-thenoyl)propyl]-4-(4-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 245 – 246.4°C

1-[γ-(2-thenoyl)propyl]-4-(4-methoxyphenyl)piperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 232 - 236°C

1-[γ-(2-thenoyl)propyl]-3α-methyl-4-phenylpiperidine-4-(N,N,-diethyl)carboxamide. With oxalate, mp about 149 – 153.2°C

1-[γ-(2-thenoyl)propyl]-3β-methyl-4-phenylpiperidine-4-(N,N-diethyl)carboxamide hydrochloride; mp about 193.2 – 194.5°C

1-[γ-(2-thenoyl)propyl]-4-(4-tolyl)-4-carboxypiperidine piperidide hydrochloride; mp about 243.5 - 245°C

1-[γ-(2-thenoyl)propyl]-3α-methyl-4-phenyl-4-carboxypiperidine piperidide. Its oxalate melts at about 184 - 187°C

1-[γ-(2-thenoyl)propyl]-3β-methyl-4-phenyl-4-carboxypiperidine piperidide hydrochloride; mp about 209 - 210°C

1-[γ-(2-thenoyl)propyl]-3β-methyl-4-phenyl-4-carboxypiperidine piperidide hydrochloride

1-[γ-(2-thenoyl)propyl]-4-phenyl-4-carboxypiperidine pyrrolidide; mp about 125.4 - 127°C. With hydrochloride, mp about 229 - 235°C

1-[γ-(2-thenoyl)propyl]-3β-methyl-4-phenyl-4-carboxypiperidine pyrrolidide hydrochloride; mp about 231.5 - 232°C

1-[γ-(2-thenoyl)propyl]-4-(3-tolyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 194.8 – 195.8°C. The oxalate melts at about 205 - 206°C

1-[γ-(2-thenoyl)propyl]-4-(4-tolyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 231 – 232.5°C

1-[γ-(2-thenoyl)propyl]-4-(4-fluorophenyl)-piperidine-4-(N,N-dimethyl)carboxamide. The oxalate melts at about 218 - 219°C

1-[γ-(2-thenoyl)propyl]-4-(3-methoxyphenyl)piperidine-4-(N,N-dimethyl)carboxamide. The oxalate melts at about 182 - 184°C

1-[γ-(2-thenoyl)propyl]-4-(4-ethylphenyl)4-carboxypiperidine pyrrolidide oxalate; mp about 184.6 – 185.6°C

1-[γ-(2-thenoyl)propyl]-4-(3-methoxyphenyl)-4-carboxypiperidine pyrrolidide; mp about 213.5 – 214.5°C

1-[γ-(2-thenoyl)propyl]-4-(4-fluorophenyl)-4-carboxypiperidine morpholide oxalate. mp about 222.5 – 223.5°C

1-[γ-(2-thenoyl)propyl]-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 233.5 – 235.5°C

1-[γ-(2-thenoyl)propyl]-4-(4-methoxyphenyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 174 - 178°C

1-[γ-(2-thenoyl)propyl]-3β-methyl-4-phenyl-4-carboxypiperidine morpholide hydrochloride; mp about 235 - 238°C

1-[γ-(2-thenoyl)propyl]-4-(3-tolyl)-4-carboxypiperidine morpholide hydrochloride; mp about 237 - 240°C

1-[γ-(2-thenoyl)propyl]-4-(4-tolyl)-4-carboxypiperidine morpholide hydrochloride; mp about 245 - 247°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-carboxamide hydrochloride; mp about 250.6 – 252°C with decomposition

1-[γ-(4-fluorobenzoyl)propyl]-3α-methyl-4-phenylpiperidine-4-carboxamide hydrochloride; mp about 229.5 - 231°C

1-[γ-(4-fluorobenzoyl)propyl]-3β-methyl-4-phenylpiperidine carboxamide; mp about 169.6 - 171°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-tolyl)-piperidine-4-carboxamide; mp about 145 – 148.6°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-ethylphenyl)piperidine-4-carboxamide

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-(N-methyl)carboxamide; mp about 143 - 144°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-(N-phenyl)carboxamide. Its oxalate melts at about 202.5°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-(N-benzyl)carboxamide hydrochloride; mp about 231.5 – 232.8°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide; mp about 119 - 120°C

1-[γ-(4-fluorobenzoyl)propyl]-3α-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide. Its oxalate melts at about 168.4 – 169.8°C with decomposition

1-[γ-(4-fluorobenzoyl)propyl]-3β-methyl-4-phenylpiperidine-4-(N,N-dimethyl)carboxamide hydrochloride; mp about 203.2 – 204.2°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-tolyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 122.5 – 123.5°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-tolyl)-piperidine-4-(N,N-dimethyl)carboxamide; mp about 132.6 - 135°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide; mp about 135 - 137°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-methoxyphenyl)piperidine-4-(N,N-dimethyl)carboxamide. Its oxalate melts at about 160 - 168°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-(N,N-diethyl)carboxamide; mp about 81 – 83.4°C

1-[γ-(4-fluorobenzoyl)propyl]-3α-methyl-4-phenylpiperidine-4-(N,N-diethyl)carboxamide. Its oxalate melts at about 161 - 165°C

1-[γ-(4-fluorobenzoyl)propyl]-3β-methyl-4-phenylpiperidine-4-(N,N-diethyl)carboxamide hydrochloride; mp about 179 – 180°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-(N-methyl)-4-(N-phenyl)carboxamide. With oxalate, mp about 211 - 212°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine piperidide; mp about 102.5 – 103.5°C

1-[γ-(4-fluorobenzoyl)propyl]-3α-methyl-4-carboxypiperidine piperidide oxalate; mp about 173 - 176°C

1-[γ-(4-fluorobenzoyl)propyl]-3β-methyl-4-phenyl-3-carboxypiperidine piperidide; mp about 88 - 89°C

1-[ω-(4-fluorobenzoyl)propyl]-3β-methyl-4-phenyl-4-carboxypiperidine piperidide

1-[γ-(4-fluorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine pyrrolidide; mp about 104 – 105.2°C

1-[γ-(4-fluorobenzoyl)propyl]-3α-methyl-4-phenyl-4-carboxypiperidine pyrrolidide oxalate; mp about 188.4 – 189.6°C

1-[γ-(4-fluorobenzoyl)propyl]-3β-methyl-4-phenyl-4-carboxypiperidine pyrrolidide; mp about 100.2 - 102°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-tolyl)-4-carboxypiperidine pyrrolidide; mp about 93.8 – 94.8°C. The oxalate melts at about 209 – 210.5°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-tolyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 143.4 – 146.8°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-fluorophenyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 199.5 - 201°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 212 - 213°C

1-[γ-(4-chlorobenzoyl)propyl]-3α-methyl-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 213 - 214°C

1-[γ-(4-iodobenzoyl)propyl]-3α-methyl-4-(4-chlorphenyl)-4-carboxypiperidine pyrrolidide hydrochloride.

1-[γ-(4-fluorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine morpholide hydrochloride; mp about 255 - 257°C

1-[γ-(4-fluorobenzoyl)propyl]-3α-methyl-4-phenyl-4-carboxypiperidine morpholide; mp about 119 – 120°C

1-[γ-(4-fluorobenzoyl)propyl]-3β-methyl-4-phenyl-4-carboxypiperidine morpholide hydrochloride; mp about 203.5 - 205°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-methoxyphenyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 218.5 – 219.5°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-chlorophenyl)-4-carboxypiperidine pyrrolidide oxalate.

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-ethylphenyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 198 - 199°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine-2,6-dimethylmorpholide oxalate; mp about 186 - 187°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-tolyl)-4-carboxypiperidine morpholide hydrochloride; mp about 239 – 240.5°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-tolyl)-4-carboxypiperidine morpholide hydrochloride; mp about 226.5 – 229.3°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-trifluoromethylphenyl)-4-carboxypiperidine morpholide hydrochloride

1-[γ-(2-theonyl)propyl]-4-(4-ethylphenyl)piperidine-4-(N,N-dimethyl)carboxamide. The oxalate melts at about 209.5 – 210.2°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-ethylphenyl)-4-carboxypiperidine morpholide oxalate; mp about 197.5 – 198.5°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-fluorophenyl)-4-carboxypiperidine morpholide; mp about 131 - 132°C. The oxalate melts at about 210 - 213°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-fluorophenyl)-4-carboxypiperidine-2-methylmorpholide oxalate.

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-fluorophenyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 188.3 - 195°C with decomposition

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-methoxyphenyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 196 – 198.6°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenylpiperidine-4-(N-isopropyl)carboxamide; mp about 153.5 - 155°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine-4-phenylpiperazide; mp about 165 – 166.2°C

1-[γ-(4-fluorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine piperazide

1-[γ-(4-fluorobenzoyl)propyl]-4-(4-ethylphenyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 185.6 – 187.4°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 193.5 - 196°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-methoxyphenyl)-4-carboxypiperidine morpholide oxalate; mp about 218.5 – 219.6°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(2-thienyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 192 - 194°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(2,4-xylyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 159.6 – 163.6°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(2,4-xylyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 164.4 – 166.4°C

1-[γ-(2-thenoyl)propyl]-3α-methyl-4-(4-chlorophenyl)-4-carboxypiperidine pyrrolidide hydrochloride; mp about 223.5 – 225.5°C

1-[γ-(2-thenoyl)propyl]-4-(4-fluorophenyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 204 - 210°C

1-[γ-(2-thenoyl)propyl]-4-(4-fluorophenyl)-4-carboxypiperidine pyrrolidide; mp about 100.4 – 103.2°C

1-[γ-(2-thenoyl)propyl]-4-(2-thienyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 175 - 180°C

1-[γ-(2-thenoyl)propyl]-4-(3-chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 197 – 198.5°C

1-[γ-(4-fluorobenzoyl)propyl]-4-(3-chlorophenyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 217 - 218°C

1-[γ-(2-thenoyl)propyl]-4-(4-ethylphenyl)-4-carboxypiperidine morpholide oxalate; mp about 206.5 – 207.5°C

1-[γ-(2-thenoyl)propyl]-4-(3-methoxyphenyl)-4-carboxypiperidine morpholide hydrochloride; mp about 217 – 222.5°C

1-(γ-benzoylpropyl)-4-(3-chlorphenyl)piperidine-4-(N,N-dimethyl)carboxamide oxalate; mp about 203 - 204°C

1-(δ-benzoylbutyl)-4-phenyl-4-carboxypiperidine pyrrolidide oxalate; mp about 187 - 188°C

1-(γ-benzoylpropyl)-4-(3-chlorophenyl)-4-carboxypiperidine pyrrolidide oxalate; mp about 208 – 209.3°C

1-[γ-(4-chlorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine pyrrolidide oxalate; mp about 202.5 – 203.5°C

Example 7

By substituting 3-xylene and 4-xylene in the method of preparation of example 1, γ-chloro-2,4-dimethylbutyrophenone (Bp about 140 - 146°C at 5 mm pressure) and γ-chloro-2,5-dimethylbutyrophenone (Bp about 142 - 148°C at 7 mm pressure) are obtained.

A mixture of 4.2 parts γ-chloro-2,5-dimethylbutyrophenone, 6 parts 4-phenyl-4-carboxypiperidine pyrrolidide, 12 parts sodium carbonate, 0.1 part potassium iodide and 280 parts 4-methyl-2-pentanone is boiled under reflux for 59 hours and then filtered. The filtrate is evaporated and the residue dissolved in 2-propanol. Oxalic acid in 2-propanol is added to the solution. The precipitate is collected on a filter, washed with acetone and then recrystallized from methanol, obtaining 1-[γ-(2,5-dimethylbenzoyl)propyl]-4-phenyl-4-carboxypiperidine pyrrolidide oxalate with mp 183.6 – 184°C.

By substituting appropriate starting products in the preparation method suitable for this, one obtains

1-[γ-(2,4-dimethylbenzoyl)propyl]-4-phenyl-4-carboxypiperidine pyrrolidide oxalate (mp 186.5 – 187.5°C) and

1-[γ-(2,4-dimethylbenzoyl)propyl]-4-(4-tolyl)-4-carboxypiperidine pyrrolidide oxalate.

Claims

1. Method for preparation of a substance with the substance

[please refer to figure in original document -- translator's note]

in which Alk is an alkylene radical with 3 to 6 carbon atoms,

Ar is a phenyl, alkylphenyl, xylyl, halophenyl, methoxyphenyl or thienyl radical,

Ar' is a phenyl, alkylphenyl, xylyl, halophenyl, methoxyphenyl or trifluoromethylphenyl radical,

R is an NH_2, NH-alkyl, N-$(alkyl)_2$, aniline, N(CH_3)-phenyl, benzylamino, pyrrolidino, piperidino, morpholino, methylmorpholino, dimethylmorpholino, piperazino or phenylpiperazino radical, and

X is equal to hydrogen or a methyl radical, with the characteristic that a substance with the formula

Ar-CO-Alk-halogen

is condensed with at least one equivalent of a substance with the formula

[please refer to figure in original document -- translator's note]

in which Ar, Alk, X, R and Ar' have the aforementioned meaning.

2. Method for preparation of 1-(γ-benzoylpropyl)-4-(4-tolyl)-4-carboxypiperidine pyrrolidide, with the characteristic that γ-chlorobutyrophenone is condensed with at least one equivalent of 4-(4-tolyl)-4-carboxypiperidine pyrrolidide.

3. Method for preparation of 1-(γ-benzoylpropyl)-4-(3-tolyl)-4-carboxypiperidine pyrrolidide, with the characteristic that γ-chlorobutyrophenone is condensed with at least one equivalent of 4-(3-tolyl)-4-carboxypiperidine pyrrolidide.

4. Method for preparation of 1-[γ-(4-fluorobenzoyl)propyl]-4-(3-tolyl)piperidine-4-(N,N-dimethyl)carboxamide, with the characteristic that γ-chloro-4-fluorobutyrophenone is condensed with at least one equivalent of 4-(3-tolyl)piperidine-4-(N,N-dimethyl)carboxamide.

5. Method for preparation of 1-[γ-(4-fluorobenzoyl)propyl]-4-(4-chlorophenyl)piperidino-4-(N,N-dimethyl)carboxamide, with the characteristic that γ-chloro-4-fluorobutyrophenone is condensed with at least one equivalent of 4-(chlorophenyl)piperidine-4-(N,N-dimethyl)carboxamide.

6. Method for preparation of 1-[γ-(4-fluorobenzoyl)propyl]-4-(4-tolyl)-4-carboxypiperidine pyrrolidide, with the characteristic that γ-chloro-4-fluorobutyrophenone is condensed with at least one equivalent of 4-(4-tolyl)-4-carboxypiperidine pyrrolidide.

7. Method for preparation of 1-[γ-(4-fluorobenzoyl)propyl]-4-(3-tolyl)-4-carboxypiperidine pyrrolidide, with the characteristic that γ-chloro-4-fluorobutyrophenone is condensed with at least one equivalent of 4-(3-tolyl)-4-carboxypiperidine pyrrolidide.

8. Method for preparation of 1-[γ-(4-fluorobenzoyl)propyl]-4-phenyl-4-carboxypiperidine pyrrolidide, with the characteristic that γ-chloro-4-fluorobutyrophenone is condensed with at least one equivalent of 4-phenyl-carboxypiperidine pyrrolidide.

9. Method for preparation of 1-[γ-(4-fluorobenzoyl)propyl]-4-(3-methoxyphenyl)-4-carboxypiperidine pyrrolidide, with the characteristic that γ-chloro-4-butyrophenone is condensed with at least one equivalent of 4-(3-methoxyphenyl)-4-carboxypiperidine pyrrolidide.

10. Method for preparation of 1-[γ-(2-thenoyl)propyl]-4-(3-tolyl)-4-carboxypiperidine pyrrolidide, with the characteristic that 2-(γ-chlorobutyryl)thiophene is condensed with at least one equivalent of 4-(3-tolyl)-4-carboxypiperidine pyrrolidide.

11. Method for preparation of 1-[γ-(4-fluorobenzoyl)propyl]-4-(2,4-xylyl)piperidine-4-(N,N-dimethyl)carboxamide, with the characteristic that γ-chloro-4-fluorobutyrophenone is condensed with at least one equivalent of 4-(2,4-xylyl)piperidine-4-(N,N-dimethyl)carboxamide.

Gierle, March 10, 1961.

In the name of the applicant,

[signature]

Dr. jur. L. van Bauwel

Power of Attorney